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COU.1.

comprises complementary guide nucleotide sequences that hybridizes under stringent conditions to a portion of the target gene.

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3. (Amended) The method of claim 1, wherein the cell is suspended in culture.
  4. (Amended) The method of claim 1, wherein the cell is in a whole animal, such as a non-human mammal.
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9. (Amended) The method of claim 1, wherein the target gene is a genomic gene of the cell.
  10. (Amended) The method of claim 1, wherein the target gene is an heterologous gene relative to the genome of the cell, such as a pathogen gene.
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12. (Amended) The method of claim 1, wherein the cell is a primate cell.
13. (Amended) The method of claim 1, wherein the dsRNA is about 20 nucleotides in length.
14. (Amended) The method of claim 12, wherein the cell is a human cell.

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15. (Amended) The method of claim 1, wherein expression of the target gene is attenuated by at least 10 fold.
16. (Amended) An assay for identifying nucleic acid sequences responsible for conferring a particular phenotype in a cell, comprising:
  - (i) constructing a variegated library of nucleic acid sequences from a cell in an orientation relative to a promoter to produce double stranded RNA (dsRNA);
  - (ii) introducing the variegated dsRNA library into a culture of target cells;
  - (iii) identifying members of the library which confer a particular phenotype on the cell, and identifying the sequence from a cell which correspond, such as being identical or homologous, to the library member.
17. (Amended) A method of conducting a drug discovery business comprising:

- (i) identifying, by the assay of claim 16, a target gene which provides a phenotypically desirable response by introducing a dsRNA, wherein the dsRNA attenuate expression of the target gene;
  - (ii) identifying agents by their ability to inhibit expression of the target gene or the activity of an expression product of the target gene;
  - (iii) conducting therapeutic profiling of agents identified in step (ii), or further analogs thereof, for efficacy and toxicity in animals; and
  - (iv) formulating a pharmaceutical preparation including one or more agents identified in step (iii) as having an acceptable therapeutic profile.
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18. (Reiterated) The method of claim 17, including an additional step of establishing a distribution system for distributing the pharmaceutical preparation for sale, and may optionally include establishing a sales group for marketing the pharmaceutical preparation.

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19. (Amended) A method of conducting a target discovery business comprising:

- (i) identifying, by the assay of claim 16, a target gene which provides a phenotypically desirable response when inhibited by RNA interference RNAi;
  - (ii) (optionally) conducting therapeutic profiling of the target gene for efficacy and toxicity in animals; and
  - (iii). licensing, to a third party, the rights for further drug development of inhibitors of the target gene.
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20. (Reiterated) A method for attenuating expression of a target gene in a cell, comprising introducing into the cell a hairpin nucleic acid in an amount sufficient to attenuate expression of the target gene, wherein the hairpin nucleic acid comprises an inverted repeat of a nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the target gene.

21. (Reiterated) A hairpin nucleic acid for inhibiting expression of a target gene, comprising a first nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the target gene, and a second nucleotide sequence which is an complementary inverted repeat of said first nucleotide sequence and hybridizes to said first nucleotide sequence to form a hairpin structure.

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22. (Amended) The method of claim 20 or the hairpin nucleic acid of claim 21, wherein the hairpin nucleic is an hairpin RNA.
23. (Reiterated) A non-human transgenic mammal having germline and/or somatic cells comprising a transgene encoding a dsRNA construct.
24. (Reiterated) The transgenic animal of claim 23, which is chimeric for said transgene.
25. (Reiterated) The transgenic animal of claim 23, wherein said transgene is chromosomally incorporated.

Please add the following new claims:

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26. (New) The method of claim 1, wherein the dsRNA is produced by a vector.
27. (New) The method of claim 1, wherein the dsRNA is a hairpin RNA including said complementary guide sequences.
28. (New) The method of claim 1, wherein the dsRNA is selected to avoid activation of a protein kinase RNA-activated (PKR) sequence-independent response.
29. (New) The method of claim 13, wherein the dsRNA has a size of about 22 nucleotides.
30. (New) An isolated guide RNA of 20-50 nucleotides, consisting essentially of a double-stranded RNA (dsRNA) for inactivating expression of a gene, comprising a first nucleotide sequence that hybridizes under stringent conditions to a nucleotide sequence of the gene to be inactivated and a second nucleotide sequence which is complementary to said first nucleotide sequence.
31. (New) The guide RNA of claim 30, having a size of about 22 nucleotides.
32. (New) An isolated guide RNA of at least 50 nucleotides, consisting essentially of a double-stranded RNA (dsRNA) for inactivating expression of a gene, comprising a first nucleotide sequence that hybridizes under stringent conditions

to a nucleotide sequence of the gene to be inactivated and a second nucleotide sequence which is complementary to said first nucleotide sequence.

33. (New) The guide RNA of claim 32, wherein said first nucleotide sequence is at least 100 nucleotides in length.
34. (New) The guide RNA of claim 33, wherein said first nucleotide sequence is at least 400 nucleotides in length.
35. (New) The guide RNA of any of claims 30-34, wherein the dsRNA is chemically synthesized.
36. (New) The guide RNA of any of claims 30-34, wherein the dsRNA is enzymatically synthesized in vitro or in vivo.
37. (New) The isolated dsRNA of any of claims 30-34, wherein said second nucleotide sequence is a complementary inverted repeat of said first nucleotide sequence and hybridizes to said first nucleotide sequence to form a hairpin structure.
38. (New) The guide RNA of any of claims 30-34, wherein the gene to be inactivated is a mammalian gene.
39. (New) The guide RNA of claim 38, wherein the mammalian gene is a human gene.
40. (New) The guide RNA of any of claims 30-34, wherein the dsRNA is produced by an arrayed library of RNAi constructs.
41. (New) A method of generating knockout cells, comprising introducing a transgene encoding a dsRNA construct into cells which contain a target gene, wherein the target gene is inactivated by the introduced dsRNA construct.
42. (New) The method of claim 41, wherein the cells are mammalian cells.

*The claims presented above incorporate changes as indicated by the marked-up version below.*

1. (Amended) A method for attenuating expression of a target gene in ~~cultured a~~ mammalian cells, comprising introducing double stranded RNA (dsRNA) into the cells in an amount sufficient to attenuate expression of the target gene, wherein the dsRNA comprises a complementary guide nucleotide sequences that hybridizes under stringent conditions to a ~~nucleotide sequence~~ portion of the target gene.
3. (Amended) The method of claim ~~2~~ 1, wherein the cell is suspended in culture.
4. (Amended) The method of claim ~~2~~ 1, wherein the cell is in a whole animal, such as a non-human mammal.
9. (Amended) The method of claim 1 ~~or 2~~, wherein the target gene is ~~an endogenous~~ a genomic gene of the cell.
10. (Amended) The method of claim 1 ~~or 2~~, wherein the target gene is ~~an~~ heterologous gene relative to the genome of the cell, such as a pathogen gene.
12. (Amended) The method of claim 1 ~~or 2~~, wherein the cell is a primate cell, ~~such as a human cell~~.
13. (Amended) The method of claim 1 ~~or 2~~, wherein the dsRNA is ~~at least~~ about 20 nucleotides in length.
14. (Amended) The method of claim ~~13~~ 12, wherein the ~~dsRNA is at least 100 nucleotides in length~~ cell is a human cell.
15. (Amended) The method of claim 1 ~~or 2~~, wherein expression of the target gene is attenuated by at least 10 fold.
16. (Amended) An assay for identifying nucleic acid sequences responsible for conferring a particular phenotype in a cell, comprising:

- (i) constructing a variegated library of nucleic acid sequences from a cell in an orientation relative to a promoter to produce double stranded DNA RNA (dsRNA);
  - (ii) introducing the variegated dsRNA library into a culture of target cells; ~~which cells have an activated Dicer activity or Argonaut activity;~~
  - (iii) identifying members of the library which confer a particular phenotype on the cell, and identifying the sequence from a cell which correspond, such as being identical or homologous, to the library member.
17. (Amended) A method of conducting a drug discovery business comprising:
- (i) identifying, by the assay of claim 16, a target gene which provides a phenotypically desirable response ~~when inhibited by RNAi~~ by introducing a dsRNA, wherein the dsRNA attenuate expression of the target gene;
  - (ii) identifying agents by their ability to inhibit expression of the target gene or the activity of an expression product of the target gene;
  - (iii) conducting therapeutic profiling of agents identified in step ~~(b)(ii)~~, or further analogs thereof, for efficacy and toxicity in animals; and
  - (iv) formulating a pharmaceutical preparation including one or more agents identified in step (iii) as having an acceptable therapeutic profile.
19. (Amended) A method of conducting a target discovery business comprising:
- (i) identifying, by the assay of claim 16, a target gene which provides a phenotypically desirable response when inhibited by RNA interference RNAi;
  - (ii) (optionally) conducting therapeutic profiling of the target gene for efficacy and toxicity in animals; and
  - (iii). licensing, to a third party, the rights for further drug development of inhibitors of the target gene.
22. (Amended) The method of claim 20 or the hairpin nucleic acid of claim 21, wherein the hairpin nucleic is an hairpin RNA.